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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,907	10/17/2003	Piero Del Soldato	026220-00039	7509

4372 7590 01/09/2009

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EXAMINER	
CHONG, YONG SOO	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
01/09/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DCIPDocket@arentfox.com
IPMatters@arentfox.com
Patent_Mail@arentfox.com

Office Action Summary	Application No.	Applicant(s)	
	10/686,907	DEL SOLDATO ET AL.	
	Examiner	Art Unit	
	YONG S. CHONG	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 10/14/2008. Claim(s) 1-3, 6 have been cancelled. Claim(s) 4-5, 7 are pending and examined herein.

Applicant's amendments to the claims have rendered the objection to claim 4 moot, therefore hereby withdrawn.

Applicant's arguments have been fully considered but found not persuasive. The rejection of the last Office Action is maintained for reasons of record and repeated below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim(s) 4-5, 7 are rejected under 35 U.S.C. 103(a) as being obvious over Del Soldato et al. (WO 95/30641) in view of Ara et al. ("Cyclooxygenase and lipoxygenase inhibitors in cancer therapy" *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 1996, 54, 3-16).

The instant claims are directed to a method of treating gastrointestinal tumors by administering a compound of formula I, where X=O, R is subgroup VIA and formula Ia.

Del Soldato et al. disclose cyclooxygenase (COX) inhibitors (pg. 1) of the formula $A\text{-}X_1\text{-}NO_2$, where $A = R(COX_u)_t$ and X=O. A preferred compound is where R is formula Ia, where t and u are 1, and R_1 is $OCOR_3$ in the ortho position, wherein R_3 is methyl and R_2 is H. Also, $X_1\text{–}NO_2$ is a 6-membered cycloalkyene, substituted with a nitroxymethyl group at the 3 position (claims).

However, Del Soldato et al. fail to disclose specifically treating gastrointestinal tumors.

Ara et al. disclose the general teaching that cyclooxygenase inhibitors are used in cancer therapy, specifically for tumors of the colon (pg. 3, left column and pg. 6, left column).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have administered a compound of formula I, where X=O, R is subgroup VIA and formula Ia to treat gastrointestinal tumors.

A person of ordinary skill in the art would have been motivated to administer a compound of formula I, where X=O, R is subgroup VIA and formula Ia to treat

gastrointestinal tumors because: (1) both Del Soldato and Ara et al. are analogous art since they both disclose cyclooxygenase inhibitors; (2) Ara et al. disclose the general teaching that cyclooxygenase inhibitors are used in treating tumors of the colon; and (3) Del Soldato et al. disclose a compound of formula I, where X=O, R is subgroup VIA and formula Ia as a cyclooxygenase inhibitor. Therefore, the skilled artisan would have had a reasonable expectation of success in treating colon tumors by administering a compound of formula I, where X=O, R is subgroup VIA and formula Ia.

Response to Arguments

Applicant's arguments have been fully considered but found not persuasive for the reasons of record. Applicant argues nonobviousness through a showing of unexpected results through the Del Soldato Declaration filed on 10/10/2003 and again on 9/21/2007. The Declaration allegedly shows unexpected increased inhibition of precancerous cell formation in an experimental model of colon cancer by nitroderivative compounds of the presently claimed invention, as shown in Tables 1 and 2.

The Del Soldato Declaration under 37 CFR 1.132 filed 10/10/2003 and again on 9/21/2007 is insufficient to overcome the rejection of claims 4-5, 7 based upon Del Soldato et al. (WO 95/30641) in view of Ara et al. ("Cyclooxygenase and lipoxygenase inhibitors in cancer therapy" *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 1996, 54, 3-16) as set forth in the last Office action because the Del Soldato Declaration simply shows that the invention as claimed works as intended. Applicant has not explained why exactly these results are unexpected or surprising. Examiner does not

find these results as unexpected or surprising in view of the cited prior art, because there is no basis or foundation for the results to be unexpected.

It is Examiner's position that no unexpected results have been shown with respect to the elected species (NO-Asp-1). Specifically, in Table 1, going to 15% from 40% in the precancerous cell number is not unexpected, especially since a higher concentration of NO-Asp-1 (18 mg/kg) was used than in aspirin (10 mg/kg). Also, the results in Table 2 cannot be considered since there is such a large difference in concentration between NO-Asp-1 (300 μM) and aspirin (500 μM). It is suggested that Applicant provide a side-by-side comparison of the two active agents having the same dosage. It is confusing why exactly there was anti-cancer activity in Experiment 1 and not in Experiment 2 considering aspirin was used in both studies.

Furthermore, since the claimed invention recites no dosage limits, a single data point having a specific dose will not support the claimed invention reciting any dosage amounts. In this manner, the results are not commensurate with the scope of the claims. It is also suggested that multiple data points be shown to support the claimed invention.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Regarding the establishment of unexpected results or synergism, a few notable principles are well settled. The Applicant has the initial burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). It is applicant's burden to present clear and

convincing factual evidence of nonobviousness or unexpected results, i.e., side-by-side comparison with the closest prior art in support of nonobviousness for the instant claimed invention over the prior art. The claims must be commensurate in the scope with any evidence of unexpected results. See MPEP 716.02 (d). With regard to synergism, a prima facie case of synergism has not been established if the data or result is not obvious. The synergism should be sufficient to overcome the obviousness, but must also be commensurate with the scope of the claims. Further, if the Applicant provides a DECLARATION UNDER 37 CFR 1.132, it must compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case if obviousness. See MPEP 716.02 (e).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Yong S Chong/
Examiner, Art Unit 1617

YSC
/SREENI PADMANABHAN/
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